2013 Space Radiation Standing Review Panel

Status Review for:
The Risk of Acute and Late Central Nervous System Effects from Radiation Exposure,
The Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs),
The Risk Of Degenerative Tissue Or Other Health Effects From Radiation Exposure, and
The Risk of Radiation Carcinogenesis

Final Report

I. Executive Summary and Overall Evaluation

The Space Radiation Standing Review Panel (from here on referred to as the SRP) was impressed with the strong research program presented by the scientists and staff associated with NASA's Space Radiation Program Element and National Space Biomedical Research Institute (NSBRI). The presentations given on-site and the reports of ongoing research that were provided in advance indicated the potential Risk of Acute and Late Central Nervous System Effects from Radiation Exposure (CNS) and were extensively discussed by the SRP. This new data leads the SRP to recommend that a higher priority should be placed on research designed to identify and understand these risks at the mechanistic level. To support this effort the SRP feels that a shift of emphasis from Acute Radiation Syndromes (ARS) and carcinogenesis to CNS-related endpoints is justified at this point. However, these research efforts need to focus on mechanisms, should follow pace with advances in the field of CNS in general and should consider the specific comments and suggestions made by the SRP as outlined below. The SRP further recommends that the Space Radiation Program Element continue with its efforts to fill the vacant positions (Element Scientist, CNS Risk Discipline Lead) as soon as possible. The SRP also strongly recommends that NASA should continue the NASA Space Radiation Summer School. In addition to these broad recommendations, there are specific comments/recommendations noted for each risk, described in detail below.

II. Comments regarding the new Gap metrics that have been developed for the Risk of Acute and Late Central Nervous System Effects from Radiation Exposure (CNS)

- Regarding the CNS risk associated with exposure to space radiation, the SRP thinks that such risks may be real based on a summary of all of the data available now. Thus, the Research Rating for CNS should be changed from "Insufficient Data" to "Unacceptable", if results obtained in mice can be confirmed in primates and humans. In light of this, increased research resources should be directed to the CNS studies effective immediately. Considering that research resources are limited, the SRP feels that increased support for the CNS studies could be accomplished by rebalancing the ratio of support for the carcinogenesis studies vs. CNS since our understanding of the carcinogenesis risks is maturing. Increased support for CNS research should not, however, come at the expense of the support for the degenerative risks, which is also at a relatively low level.
- The evidence presented regarding the effects of low-dose heavy ions on the CNS is compelling. These results also suggest that future studies are required to further characterize these CNS

effects, determine the mechanism(s) underlying the observed alterations and to begin investigating potential countermeasures. Based upon this, the SRP has a number of specific recommendations regarding these future directions:

1. First, the initial studies have utilized a wide variety of different animal models (i.e., non-transgenic mice and rats, Alzheimer's disease transgenic models and others) and behavioral paradigms (mostly hippocampal tasks including novel object recognition, odor recognition, etc.). However, in order to further characterize the effects on the CNS and attempt to relate these findings to what might occur in humans traveling in deep space, it will ultimately be important to develop a core set of animal models and behavioral paradigms that could be effectively utilized across multiple different studies supported by NASA. This will help close the gaps identified and relate to humans as quickly as possible.
2. For animal models, initial screening and characterization of the effects of low-dose heavy ions should continue to be performed in rodents. Currently, each research group supported by NASA utilizes different species, genetic backgrounds and transgenes. There is a concern that each model will likely generate a unique response to low-dose heavy ions and will thus make it difficult to consolidate these data into a consensus risk assessment for humans. Therefore, the SRP recommends that the Human Research Program (HRP) should develop a core set of recommended rodent models, including those that most closely resemble human astronauts, especially with regards to genetic diversity that could provide novel insights into individual susceptibility (i.e., collaborative cross, outbred stocks). In addition, the SRP recommends that future animal studies begin to examine a wide variety of tissue and body fluid biomarkers that can be specifically related to the CNS effects of low-dose heavy ion exposure. Identification of such biomarkers will be critical in efforts to relate these findings to humans as quickly as possible. Following the initial screening and characterization studies in rodents, the SRP recommends that the HRP consider additional animal models to extend these findings to other species (i.e., non-human primates, micro-pigs). Finally, astronauts have developed brains, and many of the animal models use juveniles with a developing CNS, which is an entirely different paradigm. Therefore, greater consideration should be given to the maturity level of CNS models.
3. For behavioral paradigms, most of the current studies have focused on hippocampal-based tasks of learning and memory. While these studies are certainly important, the SRP recommends that the HRP also encourage research into the effects of low-dose heavy ions on behavioral paradigms focused on processing speed and retrieval (see bullet #5 below). Notably, it will be important to work together with the Behavioral Health and Performance Element in generating recommended behavioral measures in rodents that are relevant to human astronauts. Such efforts will assist in relating the findings in animal models to human astronauts and developing more reliable estimates of risk.
4. In addition to animal studies characterizing the effects of low-dose heavy ions on the CNS and mechanistic studies focused on identifying the underlying biology, NASA should also consider examining the impact of well-characterized countermeasures on CNS functions. Notably, these efforts could focus on countermeasures already being instituted (i.e., exercise, sleep), or for which there is substantial evidence that the countermeasure could be effective and rapidly deployed in humans.
5. Astronauts are highly trained, extremely smart individuals, so paradigms for acute risk should perhaps focus more on the effects of radiation on cerebral white matter and non-hippocampal based cognitive functions (e.g., reaction time, fatigue, inefficient memory

retrieval), and not so much on hippocampal-based cognitive functions such as new learning and consolidation, let alone novel object recognition. As Dr. Mike Robbins (Professor of Radiation Biology from Wake Forest University, passed away in November 2012) put it, radiation exposure causes chronic oxidative stress and inflammation, increased production of reactive oxygen species leading to lipid peroxidation, oxidation of DNA and proteins, activation of pro-inflammatory factors, and progressive loss of hippocampal-dependent and non-hippocampal dependent cognitive functions. Therefore, in the short run the crew may know what to do but how fast and efficient are they at doing it?

- Specifically for the CNS risk presentation, there was an absence of gamma-ray/X-ray comparison data in the studies highlighted. The SRP thinks that the HRP should encourage investigators to include gamma-ray/X-ray controls in all studies of HZE effects. This is important for two reasons: 1) it allows for relative biological effectiveness (RBE) calculations, and 2) assessment of CNS risks from gamma-rays/X-rays may be critical for assessing risks for the low linear energy transfer LET components of space radiation. Radiation exposures on the International Space Station (ISS) would represent one such example.
- **Countermeasures:** Countermeasures against risk do not rely totally on understanding mechanisms (although that understanding is important in the long run). There are a number of empirical measures that are known to work, as in exercise (for example, physical fitness, hippocampal and other brain region neurogenesis, working off pent-up emotions), psychostimulants to the degree that fatigue and neurobehavioral slowing are issues, watching a comedy show once in a while and laughing, etc. And, anti-emetics for nausea, and all sorts of effective medications against all sorts of symptoms.
- **Individual susceptibility for CNS:** Individual susceptibility is an issue, and researchers are encouraged to focus less on "cognitive" genes (e.g., APOE-4, COMT, BDNF) and consider the at-risk alleles of genes that might have an interaction with radiation exposure (inflammatory pathway, DNA repair, metabolizing genes). There is also a genetic dose issue – and screening people, as unpleasant as it may look, is not without precedent – particularly when the objective is protection, rather than selection.
- **Non-human primates**: Although it is a difficult to get permission to do non-human primate studies, the effects being seen in rodents on cognitive function and possible degenerative effects from simulated deep space radiation are important enough that NASA needs to know if they actually occur in primate brains. The SRP is not suggesting large studies but small "n" studies to verify if the effects both behavioral and biochemical actually do occur or are something only seen in the much smaller brains of rodents. Essentially this is a proof of principle study that the risk seen in rodents will translate to human or at least non-human primates.
- **Cancer Patients undergoing Radiotherapy with Protons and Heavy Ions Represent a unique Cohort for Studying acute CNS Effects:** Several studies carried out thus far within the Space Radiation Program Element using animal models (mainly mice) suggest that acute CNS effects impairing cognitive functions cannot be excluded after exposure to low doses of particle radiation. It is inferred that if effects of similar magnitude, with comparable radiation sensitivity, also occur in humans, they will present a serious acute risk to long duration space missions, where sizeable doses of radiation may be received by the astronauts. It will be particularly useful to analyze this risk through studies directly in humans. A daily increasing number of patients undergo treatment for brain

and head and neck tumors using C-12 and protons. During treatment of these patients, their brains are exposed to particle radiation directly or indirectly, according to a treatment plan that hits extremely well defined centers of the brain, while attempting to optimally target the tumor. Doses in the range between a few Gy up to 10 or even 20 Gy may be given in the course of such treatments. These patients represent a unique resource for studying the possible acute impairment of cognitive functions following irradiation of different centers of the brain. One can envision the recruitment as volunteers (but with a sizeable remuneration to make it attractive) in a prospective study, of patients without major impairment in mental faculties as a result of their tumor. Such individuals may be tested continuously, parallel to the course of their fractionated radiation therapy for impairment in CNS function. Several tests are conceivable for this purpose (many must actually already exist) including impairment in learning, orientation, reflexes, ability to perform calculations etc., and could be carried out minutes, hours, weeks or months after the exposure. Available, highly demanding video games may also be used for this purpose. It is likely that some of these tests will be carried out in individuals receiving radiation doses in excess to those normally expected in the space environment, albeit in only a portion of their brains. Several institutions are highly vested in this type of cancer treatment including the Heidelberg Ion Therapy Centre (HIT) facility in Heidelberg, Germany (Director: Prof. Dr. Jurgen Debues) or the National Institute of Radiological Science (NIRS) facility in Chiba, Japan (Director: Prof. Dr. Tadashi Kamada) and may have patients for inclusion in such a study. More centers are already operational in Japan and more are due to open in the coming years further increasing the cohort of patients to draw from in such studies. Similar cohorts of patients may be used in the future, when treatment improves and thus the number of survivors increases, to examine increased risk to Alzheimer's or Huntington diseases as a result of a radiation exposure. A useful control in all above studies will be selected cohorts of brain tumor patients exposed to standard high voltage X-ray radiation therapy.

- **Retrospective Analysis of CNS Impairment in Brain Tumor Patients treated with Radiation:** Useful information on CNS risks may also be gained by retrospective analysis of recorded responses of patients with brain tumors exposed to all types of radiation including protons and C-12. Records may be analyzed for indications of mental deterioration as a result of radiation therapy. A serious confounding factor in this type of study, as well as in the one proposed above, is expected to be the normal mental deterioration of the patient as a result of disease progression. This confounding factor needs to be carefully considered and controlled both in the above suggested prospective study, and when possible in a retrospective study.
- **The need for mechanistic studies:** While reading the reports of ongoing studies on the effects of heavy ions on CNS, it becomes apparent that several of them test highly complex endpoints that cannot at present be understood in a mechanistic way. As many of the studies simply test the action of radiation on such endpoints, they remain by necessity purely phenomenological. While a solution to this problem will have to await better mechanistic understanding of brain function, an effort should be made to conceive studies, which at least attempt to understand the increased efficacy of heavy ions. In the field of carcinogenesis, increased efficacy is explained by increased complexity of the damage induced in the DNA. Why are heavy ions more efficacious when CNS effects are investigated? What are the targets? Is DNA playing a role? Is damage to

membranes more important in this context? Work that will at least attempt to delineate some of these open questions is certainly highly relevant to the Space Radiation Program Element.

i. *Is the overall redirection as represented in the CNS gaps, metrics and tasks sufficient to properly address the risk?*

- The SRP suggests that a higher priority be given to study the systems biology of CNS effects at the tissue and whole organ levels, to include both neural and stromal cell damage, senescence, and death; damage to the extra-cellular matrix; and whether spatially-linked damage (micro-lesions) may define unique biological effects for HZE exposure. [The portfolio already contains studies of molecular/DNA damage in cell cultures, as well as the behavioral effects on whole organisms.]
- With respect to the gap metrics system, it is unclear how the Space Radiation Program Element derived the percent numbers that a gap would be closed by if a metric were achieved. How are these percentages calculated? Are they just estimates at this stage?
- The SRP also thinks that metrics should be action items not questions if the data are sufficient to put the risk in the red, yellow or green zone and should only be questions in the gray zone, where there are not enough data or understanding to determine if a risk exists.
- The overall approach to setting out metrics for gap closure and delineation in a series of "action" items was well received by the SRP. It will be important as this approach is applied to all gaps that the items listed in the metrics and the importance of each item is matched in solicitation language and is easily available for review by applicants. Investigators should be encouraged to address the action items in grant applications.

III. Comments regarding the Other Space Radiation Program Element Risks

- ***The Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs)***
  - Much of the work done with ARS is being done by investigators funded by the NSBRI. This division between ARS and other radiation toxicities is artificial and does not benefit NASA's overall interests. Despite these concerns, however, communications between NSBRI and NASA have improved, and there may be some benefits of having some aspects of the NASA portfolio handled by NSBRI. Since radiation studies make up a portion of the NSBRI program, further study into the general utility of NSBRI to the NASA program would require an analysis of broader scope than the SRP can provide.
  - In the Center of Acute Radiation Research (CARR) mini-pig studies they mentioned that blood endpoints did not return to normal even after a long period. It is not clear if the mini-pig is inbred or out bred and if this effect on blood cells is a likely result in the human situation?

- ***The Risk Of Degenerative Tissue Or Other Health Effects From Radiation Exposure***
  - With respect to the assumption of threshold for degenerative and some CNS effects, recent data on some endpoints is suggestive of non-deterministic effects (that is there may not be thresholds for all endpoints). The SRP suggests keeping an open mind on this issue and not expect threshold effects and encourage investigators to look at low doses to define whether endpoints are seeing stochastic or deterministic events.
  - There was some discussion by the SRP that NASA looks for or solicits models of long-term degenerative risks. Many of the examples presented to the SRP seemed to be acute or short-term models. NASA might challenge investigators to show how these models relate to long-term effects.

- ***The Risk of Radiation Carcinogenesis***
  - Small molecule studies are showing that many of the effects of radiation, for example inflammation, can be targeted and that such molecules can be given after exposure and still are effective. In the case of degenerative and CNS effects, it will be useful to follow this maturing field of study for suitable molecules to be tested with space simulating radiations. It is not clear yet that any radiation mitigator studies are able to address the cancer endpoint.

IV. Additional Comments

- The SRP strongly encourages NASA to fill the vacant positions for Element Scientist, and CNS Discipline Chair as soon as possible to facilitate timely completion of needed collaborations and experiments and to enhance the overall work of the Space Radiation Program Element as a whole. An effort should be made to attract individuals with expertise covering all facets of the program including, carcinogenesis, non-cancer effects and CNS effect.
- Small "n" studies (such as the twin study) can be very useful and inform larger studies. The SRP suggests that an "n" of three would be better (two astronauts, one in space for a less amount of time for a while back, which might address repair processes, one twin with a longer period in space and more acutely studied, and perhaps a demographically similar person with no space exposure, to see what is different). In addition, regarding the twin study and small "n" studies; there was consensus on the SRP that both the twin study and other small "n" studies should be related as much as possible to rigorous similar larger "n" studies from other sources using the same or similar endpoints.
- The SRP encourages continued use of powerful recombinant backcross mouse population models that better simulate human populations. One such mouse population model is the Collaborative Cross (http://csbio.unc.edu/CCstatus/index.py). These model populations should also be valuable in studies of the CNS.
- The SRP applauds the continued use of the National Council on Radiation Protection and Measurements (NCRP), the International Commission on Radiological Protection (ICRP), and the National Academies for occasional reviews of specific space radiation research focus areas.
- The SRP strongly supports continued yearly operation of the NASA Space Radiation Summer School at the U.S. Department of Energy's Brookhaven National Laboratory. The three-week course has been offered each summer for nine years, and provides a

critical pipeline of young experimentalists cognizant in biological effects of HZE particle exposure. The information and the feedback members of the committee received from the scientific community are uniformly positive regarding the value and the importance of the NASA Space Radiation Summer School. The NASA Space Radiation Summer School helps to attract and train young individuals in the field of radiation and helps thus maintain vigorous research activity as required to address the programmatic aims of the NASA Space Radiation Program Element. The SRP therefore feels strongly that the NASA Space Radiation Summer School needs to be preserved.

- Dose and dose rate. Many of the studies presented to the SRP from ongoing research used starting doses of 2 Gy and there seemed to be a lack of focus on doses below 1 Gy, which will be more meaningful for most situations in proposed deep space travel. Some endpoints described may not occur at lower doses. The SRP suggests the Space Radiation Program Element challenge investigators to prove endpoints are important at lower more relevant doses. On low dose rate (or fractionation) there are few studies so far. As endpoints are validated investigators should be motivated to move to chronic or fractionated exposures to make sure the effects can be seen under more chronic conditions.
- The SRP was not in agreement with the Space Radiation Program Element's plans to only focus on Food and Drug Administration (FDA)-approved drugs for countermeasure research. The SRP thinks additional approaches should be discussed in the context of what is appropriate for a deep space traveler. Current FDA-approved drugs/biologics are only aimed at acute effects of radiation. There are no drugs/biologics approved or even in the pipeline that are designed to mitigate the effects of radiation on cancer risk and/or degenerative risks. So it may make sense to begin a process to screen radio-mitigating biologics that can be given during or after an exposure for effectiveness against cancer and degenerative risks. The Space Radiation Program Element should also consider using the FDA Investigational New Drug (IND) process to evaluate promising biologics and not insist on full approval. Last, the SRP discussed and certainly encourages the Space Radiation Program Element (within the constraint of peer reviewed science) to look at other ways to mitigate radiation risks such as exercise, shielding, dietary intervention, sleep cycles, etc. It is perhaps time to begin a combined analysis of all countermeasures to determine what routes can be safely undertaken during a deep space mission and after the deep space travelers return to Earth.
- Rather than integration, the SRP thinks there should be strong "interaction" or collaboration with the other Program Elements within the HRP.
- The SRP thinks the issue of choosing the shielding to be used and its resulting spectrum of radiation spallation products is becoming critical to moving the related radiobiology forward.
- Overall individual radiosensitivity/susceptibility: Individual radiosensitivity, cancer susceptibility etc. should be considered seriously not as basis for selection, but rather from the perspective of radiation protection. Information along these lines should be generated to help NASA protect astronauts with increased radiosensitivity or cancer susceptibility. Such predisposition is highly likely for carcinogenesis, but could also be present for acute and delayed CNS effects.
- Limitations of Animal Model Systems: Diverse animal model systems have been used in the past within the NASA programs to study sensitivity to radiation at different end

points, intending to anticipate in this way human responses to similar insults. This approach is justified and valid. With results accumulating from ongoing work it is becoming increasingly evident, at times proportionally to the volume of available data, that different animal model systems can generate widely divergent radiosensitivity results, at least for certain end points. This development allows two inferences that are worth incorporating in future strategies for shaping the program. First, although the unanticipated variation in response confounds the original programmatic aim of the work, it should now be regarded by itself as one of its most valuable outcomes – i.e., without the work this limitation would not have been identified. Second, it demonstrates that animal model systems need validation for relevance to anticipated human responses before utilization in long-term, high-cost studies. Recognition of this limitation and the obvious difficulty in addressing this complication suggests that priority should be given to obtaining as much information as feasible directly in humans (see recommendations above).

- Meeting in person: The SRP feels that meeting in person is more effective than meeting through teleconference calls. The direct interactions and the personal contact, not only between the members of the SRP but also with members of the Space Radiation Program Element, NSBRI, and other NASA representatives, enables a more intense and fruitful exchange of ideas, the clarification of critical issues or of misunderstandings, thus expediting and optimizing the overall steering of the program.

V. 2013 Space Radiation Standing Review Panel Status Review: Statement of Task for the Risk of Acute and Late Central Nervous System Effects from Radiation Exposure, the Risk of Acute Radiation Syndromes Due to Solar Particle Events (SPEs), the Risk Of Degenerative Tissue Or Other Health Effects From Radiation Exposure, and the Risk of Radiation Carcinogenesis

The 2013 Space Radiation Standing Review Panel (SRP) will participate in a Status Review that will occur via a site visit meeting with the Human Research Program (HRP) Chief Scientist, Deputy Chief Scientist and members of the Space Radiation Program Element. The purpose of this review is for the SRP to:

1. Receive an update by the HRP Chief Scientist or Deputy Chief Scientist on the status of NASA's current and future exploration plans and the impact these will have on the HRP.

2. Receive an update on any changes within the HRP since the 2012 SRP meeting.

3. Receive an update by the Element or Project Scientist(s) on progress since the 2012 SRP meeting.

    a. The Space Radiation Element is in the process of redirecting their research program for their Acute, Cancer, Central Nervous Central (CNS), and Degenerative (Degen) risks.
    b. Gap metrics have been developed for CNS as a test case for new direction.
        i. Is the overall redirection as represented in the CNS gaps, metrics and tasks sufficient to properly address the risk?
    c. Receive an update on Acute, Cancer and Degen risks.

4. Participate in a discussion with the HRP Chief Scientist, Deputy Chief Scientist, and the Element regarding possible topics to be addressed at the next SRP meeting

The 2013 Space Radiation SRP will produce a report/comments from this status review within 30 days of the 2013 update. These comments will be submitted to the HRP Chief Scientist and copies will be provided to the Space Radiation Program Element and also made available to the other HRP Elements. The 2013 SRP Final Report will be made available on the HRR website (http://humanresearchroadmap.nasa.gov/).

VI. 2013 Space Radiation Standing Review Panel Roster

Panel Chair:

Gayle Woloschak, Ph.D.
Northwestern University
Departments of Radiation Oncology,
Radiology, and Cell & Molecular Biology
303 E. Chicago Avenue
Ward 13-002
Chicago, IL 60611
Ph: 312-503-4322
Email: **g-woloschak@northwestern.edu**

Panel Members:

Colin Hill, Ph.D.
University of Southern California
Radiation Oncology
1303 N. Mission Road
CRL 208B, 9171
Los Angeles, CA 90033
Ph: 323-224-7783
Email: **ckhill@usc.edu**

George Iliakis, Ph.D.
University of Duisburg-Essen Medical School
Institute of Medical Radiation Biology
Hufelandstr. 55
45122 Essen
GERMANY
Ph: +49-201-723 4152/3
Email: **Georg.Iliakis@uk-essen.de**

Bruce Lamb, Ph.D.
The Cleveland Clinic Foundation
Neurosciences, NC30
9500 Euclid Avenue, NC30
Cleveland, OH 44195
Ph: 216-444-3592
Email: **lambb@ccf.org**

Noelle Metting, Sc.D.
U.S. Department of Energy
Low Dose Radiation Research Program
SC-72/Germantown Building
1000 Independence Avenue, SW
Washington, DC 20585
Ph: 301-903-8309
Email**: noelle.metting@science.doe.gov**

Christina Meyers, Ph.D., ABPP
M.D. Anderson Cancer Center
Professor and Chief of Neuropsychology (retired)
M.D. Anderson Cancer Center
10064 Keuss Farms Drive
Richwoods, MO 63071
Ph: 573-678-2420
Email: **cameyers53@yahoo.com**

Raymond Meyn, Ph.D.
The University of Texas M.D. Anderson
Cancer Center
Experimental Radiation Oncology
Unit 066
1515 Holcombe Boulevard
Houston, TX 77030
713-792-3424 (p)
Email: **rmeyn@mdanderson.org**